

10/562142

JC10 Rec'd PCT/PTO 23 DEC 2005

## PYRROLO-DIHYDROISOQUINOLINE DERIVATIVES AS PDE10 INHIBITORS

**Field of application of the invention**

The invention relates to the use of a certain structure-element as an integral part of the overall structure of pyrrolodihydroisoquinoline compounds, which inhibit PDE10 and can be used in the pharmaceutical industry for the production of pharmaceutical compositions.

**Known technical background**

The International applications WO 02/48144, WO 03/014115, WO 03/014116, WO 03/014117 and WO 03/051877 disclose pyrrolodihydroisoquinoline derivatives with PDE10 inhibitory activity. Said International applications are incorporated by reference into the specification of the present invention in their entirety for all purposes.

The European application EP 1250923 discloses the use of selective PDE10 inhibitors in general, and papaverine in particular, for the treatment of certain neurologic and psychiatric disorders.

Said European application is incorporated by reference into the specification of the present invention in its entirety for all purposes.

Additionally, the US application US 2003/0008806 likewise disclose the use of selective PDE10 inhibitors in general, and papaverine in particular, for the treatment of certain neurologic and psychiatric disorders; said US application is incorporated by reference into the specification of the present invention in its entirety for all purposes.

Yet additionally, the US application US 2003/0018047 also disclose the use of selective PDE10 inhibitors in general, and papaverine in particular, for the treatment of certain neurologic and psychiatric disorders; said US application is incorporated by reference into the specification of the present invention in its entirety for all purposes.

The US patent US 5965575 discloses pyrrolodihydroisoquinoline derivatives as 5HT<sub>1B</sub> antagonists.

The International application WO 03/000269 disclose the use of PDE10A inhibitors for the treatment of neurodegenerative diseases, especially Parkinson's disease.

**Description of the invention**

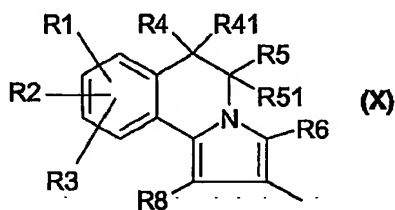
It has now been found that the structure-element per se, which is specified in greater details below, as well as its use as integral part of the overall structure of compounds, which inhibit PDE10, differ profoundly from prior art. Thus, said novel structure-element differs from prior art by unanticipated, sophisticated and originaive structural features and its inherent, surprising and particularly advantageous function as integral part of the overall structure of compounds which inhibit PDE10.

- 2 -

In a first aspect, the present invention provides structure-activity principles for use in the design of PDE10 inhibitors of the pyrrolodihydroisoquinoline class with surprising and particularly advantageous properties.

In a more detailed aspect, the present invention provides structure-activity principles for use in the design of PDE10 inhibitors of the pyrrolodihydroisoquinoline class with improved effectiveness and/or improved selectivity.

Thus, a special aspect (special aspect A) of the present invention is the use of a structure-element of the formula X



in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy,

R4 is hydrogen,

R41 is hydrogen,

R5 is hydrogen or 1-4C-alkyl, and

R51 is hydrogen or 1-4C-alkyl,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkoxycarbonyl, and

R51 is hydrogen,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is cyano, and

R51 is hydrogen,

or

R4 and R5 together form a 3-4C-alkylene bridge and R41 and R51 are both hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl, and

- 3 -

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is cyano, or -C(O)-OR9, in which

R9 is 1-4C-alkyl;

under the proviso, that,

when R8 is -C(O)-OR9, in which

R9 is 1-4C-alkyl,

then R5 is other than hydrogen;

as integral part of the overall structure of compounds which inhibit PDE10.

An embodiment of special aspect A of the present invention refers to the use of a structure-element of the formula X

in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy,

R4 is hydrogen,

R41 is hydrogen,

R5 is hydrogen or 1-4C-alkyl, and

R51 is hydrogen or 1-4C-alkyl,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkoxycarbonyl, and

R51 is hydrogen,

or

R4 and R5 together form a 3-4C-alkylene bridge and R41 and R51 are both hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl, and

R612 is hydrogen or 1-4C-alkyl, or

- 4 -

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is cyano, or -C(O)-OR9, in which

R9 is 1-4C-alkyl;

under the proviso, that,

when R8 is -C(O)-OR9, in which

R9 is 1-4C-alkyl,

then R5 is other than hydrogen;

as integral part of the overall structure of compounds which inhibit PDE10.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

2-4C-Alkyl represents a straight-chain or branched alkyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl radical.

1-6C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 6 carbon atoms. Examples which may be mentioned are the hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl or methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

2-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy radical.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

- 5 -

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkylmethoxy represents cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

3-7C-Cycloalkyl-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylethyl and the cyclohexylmethyl radicals.

1-4C-Alkoxy-2-4C-alkoxy represents one of the abovementioned 2-4C-alkoxy radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-methoxyethoxy, 2-ethoxyethoxy and the 2-isopropoxyethoxy radicals.

1-4C-Alkoxy-2-4C-alkyl represents one of the abovementioned 2-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-methoxyethyl and the 2-isopropoxyethyl radicals.

1-4C-Alkoxy-carbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxycarbonyl and ethoxycarbonyl radicals.

3-4C-Alkylene is a straight-chain alkylene radical such as, for example, the trimethylene ( $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ) or the tetramethylene ( $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ) radical.

Halogen within the meaning of the invention is bromine and, preferably, chlorine and fluorine.

Hydroxy-2-4C-alkyl stands for one of the abovementioned 2-4C-alkyl radicals which is substituted by a hydroxyl group. Examples which may be mentioned are the 2-hydroxyethyl and 3-hydroxypropyl radicals.

Amino-2-4C-alkyl stands for one of the abovementioned 2-4C-alkyl radicals which is substituted by an amino group. Examples which may be mentioned are the 2-aminoethyl and 3-aminopropyl radicals.

In addition to the nitrogen atom, mono- or di-1-4C-alkylamino radicals contain one or two of the abovementioned 1-4C-alkyl radicals. Di-1-4C-alkylamino is to be emphasized and here, in particular, dimethyl-, diethyl- and diisopropylamino.

Mono- or Di-1-4C-alkylamino-2-4C-alkyl stands for one of the abovementioned 2-4C-alkyl radicals which is substituted by one of the abovementioned mono- or di-1-4C-alkylamino groups. Examples which may be mentioned are the 2-dimethylaminoethyl and 3-dimethylaminopropyl radicals.

- 6 -

Het1 refers to a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom. Examples for Het2 include e.g. piperidin-1-yl, 4-methyl-piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholin-4-yl, pyrrolidin-1-yl, piperazin-1-yl, imidazolidin-1-yl, thiomorpholin-4-yl, homopiperidin-1-yl, homopiperazin-1-yl, 4-N-(1-4C-alkyl)-homopiperazin-1-yl or piperazinyl substituted on a ring nitrogen atom by R613 [4-N-(R613)-piperazin-1-yl] such as, for example, 4-N-(1-4C-alkyl)-piperazin-1-yl, 4-N-(hydroxy-2-4C-alkyl)-piperazin-1-yl, 4-N-(dimethylamino-2-4C-alkyl)-piperazin-1-yl, 4-N-(3-6C-cycloalkyl)-piperazin-1-yl, 4-N-formyl-piperazin-1-yl, 4-N-(pyridin-4-yl)-piperazin-1-yl, 4-N-(pyrimidin-2-yl)-piperazin-1-yl or 4-N-(3-6C-cycloalkylmethyl)-piperazin-1-yl.

N-(1-4C-alkyl)-piperazinyl stands for the piperazin-1-yl radical substituted by one of the abovementioned 1-4C-alkyl radicals on the 4-N ring nitrogen atom.

Constituents which are substituted as described herein may be substituted, unless otherwise noted, at any possible position.

Thus, the substituents R1, R2 and/or R3 may be attached, unless otherwise noted, at any position of the benzo moiety of the pyrrolodihydroisoquinoline ring.

A subaspect (subaspect a1) of the special aspect a according to this invention worthy to be mentioned is the use of a structure-element of the formula X,

in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy,

R4 is hydrogen,

R41 is hydrogen,

R5 is ethyl or, in particular, methyl,

R51 is hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

- 7 -

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is cyano,

as integral part of the overall structure of compounds which inhibit PDE10.

A subaspect (subaspect a2) of the special aspect A according to this invention more worthy to be mentioned is the use of a structure-element of the formula X,

in which

R1 is halogen or 1-4C-alkoxy,

R2 is hydrogen, halogen or 1-4C-alkoxy,

R3 is 1-4C-alkoxy,

R4 is hydrogen,

R41 is hydrogen,

R5 is hydrogen, methyl or ethyl,

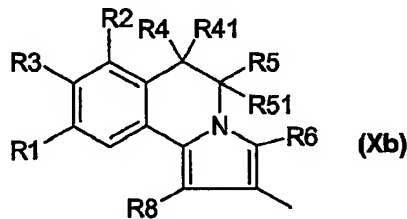
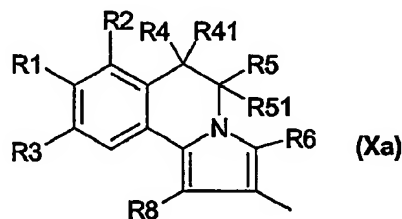
R51 is hydrogen,

R6 is methyl, ethyl or methoxycarbonyl ethyl,

R8 is cyano,

as integral part of the overall structure of compounds which inhibit PDE10.

A subaspect (subaspect a3) of the special aspect A according to this invention in particular worthy to be mentioned is the use of a structure-element of the formula Xa or Xb



In which

as a first alternative,

R1 is chlorine or fluorine,

R2 is hydrogen,

R3 is methoxy or ethoxy,

or, as a second alternative,

- 8 -

R1 is methoxy or ethoxy,  
R2 is hydrogen,  
R3 is methoxy or ethoxy,  
or, as a third alternative,  
R1 is chlorine or fluorine,  
R2 is methoxy or ethoxy,  
R3 is methoxy or ethoxy,  
or, as a fourth alternative,  
R1 is methoxy or ethoxy,  
R2 is chlorine or fluorine,  
R3 is methoxy or ethoxy,  
or, as a fifth alternative,  
R1 is methoxy or ethoxy,  
R2 is methoxy or ethoxy,  
R3 is methoxy or ethoxy;  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is ethyl or, in particular, methyl,  
R51 is hydrogen,  
R6 is methyl, ethyl or methoxycarbonylethyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

A subaspect (subaspect a4) of the special aspect A according to this invention in more particular worthy to be mentioned is the use of a structure-element of the formula Xa, in which

R1 is methoxy,  
R2 is hydrogen,  
R3 is methoxy,  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is methyl,  
R51 is hydrogen,  
R6 is methyl or methoxycarbonylethyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

Another subaspect (subaspect b1) of the special aspect A according to this invention worthy to be mentioned is the use of a structure-element of the formula X,



- 9 -

In which

- R1 is halogen or 1-4C-alkoxy,
- R2 is hydrogen, halogen or 1-4C-alkoxy,
- R3 is 1-4C-alkoxy,
- R4 is hydrogen,
- R41 is hydrogen,
- R5 is methyl or ethyl,
- R51 is hydrogen,
- R6 is methyl, ethyl or methoxycarbonyl ethyl,
- R8 is -C(O)-OR9, in which
- R9 is 1-4C-alkyl,

as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect b2) of the special aspect A according to this invention more worthy to be mentioned is the use of a structure-element of the formulae Xa or Xb,

in which

as a first alternative,

- R1 is chlorine or fluorine,
- R2 is hydrogen,
- R3 is methoxy or ethoxy,

or, as a second alternative,

- R1 is methoxy or ethoxy,
- R2 is hydrogen,
- R3 is methoxy or ethoxy,

or, as a third alternative,

- R1 is chlorine or fluorine,
- R2 is methoxy or ethoxy,
- R3 is methoxy or ethoxy,

or, as a fourth alternative,

- R1 is methoxy or ethoxy,
- R2 is chlorine or fluorine,
- R3 is methoxy or ethoxy,

or, as a fifth alternative,

- R1 is methoxy or ethoxy,
- R2 is methoxy or ethoxy,
- R3 is methoxy or ethoxy,
- R4 is hydrogen,
- R41 is hydrogen,
- R5 is ethyl or, in particular, methyl,
- R51 is hydrogen,

- 10 -

R6 is methyl, ethyl or methoxycarbonylethyl,  
R8 is -C(O)-OR9, in which  
R9 is 1-4C-alkyl,  
as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect b3) of the special aspect A according to this invention in particular worthy to be mentioned is the use of a structure-element of the formula Xa, in which

R1 is methoxy,  
R2 is hydrogen,  
R3 is methoxy,  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is methyl,  
R51 is hydrogen,  
R6 is methyl or methoxycarbonylethyl,  
R8 is -C(O)-OR9, in which  
R9 is 1-4C-alkyl,  
as integral part of the overall structure of compounds which inhibit PDE10.

Regarding the aforementioned subaspects according to the present invention, the subaspects a1, a2, a3 and a4 are to be emphasized.

The subaspects a2, a3 and a4 are in particular to be emphasized, and the subaspects a3 and, especially, a4 are in more particular to be emphasized.

Another subaspect (subaspect c1) of the special aspect A according to this invention worthy to be mentioned is the use of a structure-element of the formula Xa or Xb, in which

R1 is 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,  
R2 is hydrogen or halogen,  
R3 is 1-4C-alkoxy,  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is 1-4C-alkyl or cyano,  
R51 is hydrogen,  
R6 is 1-4C-alkyl, or 1-4C-alkyl substituted by 1-4C-alkoxycarbonyl,  
R8 is -C(O)-OR9, in which  
R9 is 1-4C-alkyl,  
as integral part of the overall structure of compounds which inhibit PDE10.

- 11 -

A further subaspect (subaspect c2) of the special aspect A according to this invention more worthy to be mentioned is the use of a structure-element of the formula Xa or Xb,

in which

- R1 is 1-4C-alkoxy,
- R2 is hydrogen or halogen,
- R3 is 1-4C-alkoxy,
- R4 is hydrogen,
- R41 is hydrogen,
- R5 is 1-4C-alkyl or cyano,
- R51 is hydrogen,
- R6 is 1-4C-alkyl, or 1-4C-alkyl substituted by 1-4C-alkoxycarbonyl,
- R8 is -C(O)-OR9, in which
- R9 is 1-4C-alkyl,

as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect c3) of the special aspect A according to this invention more worthy to be mentioned is the use of a structure-element of the formula Xa or Xb,

in which

- R1 is 1-2C-alkoxy,
- R2 is hydrogen, chlorine or fluorine,
- R3 is 1-2C-alkoxy,
- R4 is hydrogen,
- R41 is hydrogen,
- R5 is 1-2C-alkyl or cyano,
- R51 is hydrogen,
- R6 is 1-2C-alkyl, or 1-2C-alkyl substituted by 1-2C-alkoxycarbonyl,
- R8 is -C(O)-OR9, in which
- R9 is 1-2C-alkyl,

as integral part of the overall structure of compounds which inhibit PDE10.

Another subaspect (subaspect d1) of the special aspect A according to this invention worthy to be mentioned is the use of a structure-element of the formula Xa or Xb,

in which

- R1 is 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,
- R2 is hydrogen or halogen,
- R3 is 1-4C-alkoxy,
- R4 is hydrogen,
- R41 is hydrogen,

- 12 -

R5 is hydrogen, 1-4C-alkyl or cyano,  
R51 is hydrogen,  
R6 is 1-4C-alkyl, or 1-4C-alkyl substituted by 1-4C-alkoxycarbonyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect d2) of the special aspect A according to this invention more worthy to be mentioned is the use of a structure-element of the formula Xa or Xb,  
in which

R1 is 1-4C-alkoxy,  
R2 is hydrogen or halogen,  
R3 is 1-4C-alkoxy,  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is hydrogen, 1-4C-alkyl or cyano,  
R51 is hydrogen,  
R6 is 1-4C-alkyl, or 1-4C-alkyl substituted by 1-4C-alkoxycarbonyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect d3) of the special aspect A according to this invention further more worthy to be mentioned is the use of a structure-element of the formula Xa or Xb,  
in which

R1 is 1-2C-alkoxy,  
R2 is hydrogen, chlorine or fluorine,  
R3 is 1-2C-alkoxy,  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is hydrogen, 1-2C-alkyl or cyano,  
R51 is hydrogen,  
R6 is 1-2C-alkyl, or 1-2C-alkyl substituted by 1-2C-alkoxycarbonyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect d4) of the special aspect A according to this invention still further more worthy to be mentioned is the use of a structure-element of the formula Xa or Xb,  
in which

R1 is 1-2C-alkoxy,  
R2 is hydrogen, chlorine or fluorine,  
R3 is 1-2C-alkoxy,

- 13 -

R4 is hydrogen,  
R41 is hydrogen,  
R5 is 1-2C-alkyl or cyano,  
R51 is hydrogen,  
R6 is 1-2C-alkyl, or 2-methoxycarbonylethyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect d5) of the special aspect A according to this invention yet further more worthy to be mentioned is the use of a structure-element of the formula Xa or Xb, in which

R1 is 1-2C-alkoxy,  
R2 is chlorine or fluorine,  
R3 is 1-2C-alkoxy,  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is hydrogen, 1-2C-alkyl or cyano,  
R51 is hydrogen,  
R6 is 1-2C-alkyl, or 2-methoxycarbonylethyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

A further subaspect (subaspect d6) of the special aspect A according to this invention still yet further more worthy to be mentioned is the use of a structure-element of the formula Xa or Xb, in which

R1 is methoxy,  
R2 is hydrogen, chlorine or, particularly, fluorine,  
R3 is methoxy,  
R4 is hydrogen,  
R41 is hydrogen,  
R5 is methyl or cyano,  
R51 is hydrogen,  
R6 is methyl, or 2-methoxycarbonylethyl,  
R8 is cyano,  
as integral part of the overall structure of compounds which inhibit PDE10.

Within the meaning of this invention, a particular subaspect (subaspect e1) of the special aspect A of this invention is the use of a structure-element selected from the group consisting of those structure-elements of the formula Xa,

- 14 -

in which

R1 is methoxy,

R3 is methoxy,

R4 is hydrogen,

R41 is hydrogen,

R51 is hydrogen,

and in which the following combinations 1.) to 50.) of the substituent meanings for R2, R5, R6 and R8 of Table 1 apply:

Table 1:

	R2	R5	R6	R8
1.)	hydrogen	methyl	methyl	cyano
2.)	hydrogen	methyl	methyl	ethoxycarbonyl
3.)	hydrogen	methyl	2-methoxycarbonylethyl	cyano
4.)	hydrogen	methyl	2-methoxycarbonylethyl	ethoxycarbonyl
5.)	hydrogen	hydrogen	methyl	cyano
6.)	hydrogen	hydrogen	2-methoxycarbonylethyl	cyano
7.)	fluorine	methyl	methyl	cyano
8.)	fluorine	methyl	methyl	ethoxycarbonyl
9.)	fluorine	methyl	2-methoxycarbonylethyl	cyano
10.)	fluorine	methyl	2-methoxycarbonylethyl	ethoxycarbonyl
11.)	fluorine	hydrogen	methyl	cyano
12.)	fluorine	hydrogen	2-methoxycarbonylethyl	cyano
13.)	fluorine	hydrogen	methyl	ethoxycarbonyl
14.)	fluorine	hydrogen	2-methoxycarbonylethyl	ethoxycarbonyl
15.)	hydrogen	cyano	methyl	cyano
16.)	hydrogen	cyano	methyl	ethoxycarbonyl
17.)	hydrogen	cyano	2-methoxycarbonylethyl	cyano
18.)	hydrogen	cyano	2-methoxycarbonylethyl	ethoxycarbonyl
19.)	fluorine	cyano	methyl	cyano
20.)	fluorine	cyano	methyl	ethoxycarbonyl
21.)	fluorine	cyano	2-methoxycarbonylethyl	cyano
22.)	fluorine	cyano	2-methoxycarbonylethyl	ethoxycarbonyl
23.)	chlorine	methyl	methyl	cyano
24.)	chlorine	methyl	methyl	ethoxycarbonyl
25.)	chlorine	methyl	2-methoxycarbonylethyl	cyano
26.)	chlorine	methyl	2-methoxycarbonylethyl	ethoxycarbonyl
27.)	chlorine	hydrogen	methyl	cyano
28.)	chlorine	hydrogen	2-methoxycarbonylethyl	cyano
29.)	chlorine	hydrogen	methyl	ethoxycarbonyl
30.)	chlorine	hydrogen	2-methoxycarbonylethyl	ethoxycarbonyl
31.)	chlorine	cyano	methyl	cyano
32.)	chlorine	cyano	methyl	ethoxycarbonyl
33.)	chlorine	cyano	2-methoxycarbonylethyl	cyano
34.)	chlorine	cyano	2-methoxycarbonylethyl	ethoxycarbonyl
35.)	hydrogen	methyl	methyl	methoxycarbonyl
36.)	hydrogen	methyl	2-methoxycarbonylethyl	methoxycarbonyl
37.)	fluorine	methyl	methyl	methoxycarbonyl
38.)	fluorine	methyl	2-methoxycarbonylethyl	methoxycarbonyl
39.)	fluorine	hydrogen	methyl	methoxycarbonyl
40.)	fluorine	hydrogen	2-methoxycarbonylethyl	methoxycarbonyl
41.)	hydrogen	cyano	methyl	methoxycarbonyl
42.)	hydrogen	cyano	2-methoxycarbonylethyl	methoxycarbonyl
43.)	fluorine	cyano	methyl	methoxycarbonyl

- 15 -

44.)	fluorine	cyano	2-methoxycarbonylethyl	methoxycarbonyl
45.)	chlorine	methyl	methyl	methoxycarbonyl
46.)	chlorine	methyl	2-methoxycarbonylethyl	methoxycarbonyl
47.)	chlorine	hydrogen	methyl	methoxycarbonyl
48.)	chlorine	hydrogen	2-methoxycarbonylethyl	methoxycarbonyl
49.)	chlorine	cyano	methyl	methoxycarbonyl
50.)	chlorine	cyano	2-methoxycarbonylethyl	methoxycarbonyl

whereby the combinations 1 to 7, 16, 24 and 35 are to be emphasized, and  
 whereby the combinations 1, 3, 5, 6 and 7 are to be more emphasized, and  
 whereby the combination 7 is to be in particular emphasized;  
 as integral part of the overall structure of compounds which inhibit PDE10.

A further aspect of the present invention is the use of a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, in particular in the subaspects thereto, in more particular in the subaspects emphasized above, as an integral part of the overall structure of compounds, which inhibit effectively PDE10, for use in treating disorders of the central nervous system.

A further aspect of the present invention is the use of a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, particularly, in the subaspects thereto, as an integral part of the overall structure of compounds for use in therapy.

A further aspect of the present invention is the use of a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, particularly, in the subaspects thereto, as an integral part of the overall structure of compounds, which inhibit PDE10, for use in the manufacture of pharmaceutical compositions.

A further aspect of the present invention is the use of a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, particularly, in the subaspects thereto, to provide compounds, which inhibit PDE10.

A further aspect of the present invention is a process to provide compounds, which inhibit PDE10, comprising the following steps:

a.) designing intellectually the structure of a compound comprising - as part of its overall structure - a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, in particular, in the subaspects thereto, in more particular in the subaspects emphasized above;

- 16 -

b.) synthesizing materially a compound having said designed structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

A further aspect of the present invention is a compound obtainable by the abovementioned process to provide compounds, which inhibit PDE10.

A further aspect of the present invention are compounds which inhibit effectively PDE10 and which comprise a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, particularly, in the subaspects thereto, as an integral part of their overall structures.

Consequently, compounds according to the present invention include those compounds, which comprise a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A.

A further aspect of the present invention is a method to inhibit PDE10 comprising using a compound containing -as an integral part of its overall structure- a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, particularly, in the subaspects thereto.

A further aspect of the present invention is a method for treating disorders of the central nervous system by effective inhibiting of PDE10 comprising administering to a subject in need thereof a therapeutically effective and tolerable amount of a compound having a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspects A, particularly, in the subaspects thereto, as an integral part of its overall structure.

A further aspect of the present invention is a process or method for providing PDE10 inhibitors of the pyrrolodihydroisoquinoline class with advantageous pharmacological properties (e.g. improved effectiveness) comprising the following steps:

- a.) selecting intellectually a structure of a compound of the pyrrolodihydroisoquinoline class;
- b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, in particular, in the subaspects thereto, in more particular in the subaspects emphasized above;
- c.) synthesizing materially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.



- 17 -

A further aspect of the present invention is a method for providing PDE10 inhibitors of the pyrrolodihydroisoquinoline class with advantageous properties comprising the following steps:

a.) selecting intellectually a structure of a compound of the pyrrolodihydroisoquinoline class, or, advantageously,

selecting intellectually a structure of a compound disclosed, in a first embodiment, in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or, in a second embodiment, in WO 02/48144, WO 03/014115, WO 03/014116, WO 03/014117 or WO 03/051877,

preferably a structure of a compound mentioned *expressis verbis* or individualized by way of example therein,

more preferably a structure of a compound emphasized therein and/or a structure of a compound disclosed therein with advantageous effects (e.g. advantageous PDE10 inhibiting values);

b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, in particular, in the subaspects thereto, in more particular in the subaspects emphasized above;

c.) synthesizing materially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed, in a first embodiment, in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or, in a second embodiment, in WO 02/48144, WO 03/014115, WO 03/014116, WO 03/014117 or WO 03/051877,

or analogously or similarly thereto.

A further aspect of the present invention is a compound obtainable by one of the abovementioned processes or methods for providing PDE10 inhibitors of the pyrrolodihydroisoquinoline class with advantageous properties.

A further aspect of the present invention is a method for treating disorders of the central nervous system by effective inhibiting of PDE10 comprising administering to a subject in need thereof a pharmaceutically effective and tolerable amount of a compound obtainable by the process comprising the following steps:

a.) selecting intellectually a structure of a compound of the pyrrolodihydroisoquinoline class, or, advantageously,

selecting intellectually a structure of a compound disclosed, in a first embodiment, in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or, in a second embodiment, in WO 02/48144, WO 03/014115, WO 03/014116, WO 03/014117 or WO 03/051877,

preferably a structure of a compound mentioned *expressis verbis* or individualized by way of example therein,

more preferably a structure of a compound emphasized therein and/or a structure of a compound disclosed therein with advantageous effects (e.g. advantageous PDE10 inhibiting values);

- 18 -

b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, in particular, in the subaspects thereto, in more particular in the subaspects emphasized above;

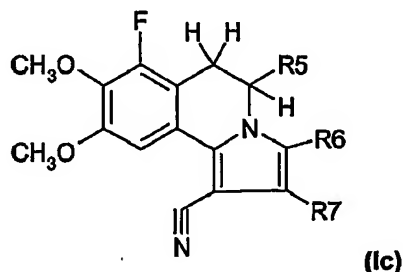
c.) synthesizing materially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed, in a first embodiment, in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or, in a second embodiment, in WO 02/48144, WO 03/014115, WO 03/014116, WO 03/014117 or WO 03/051877, or analogously or similarly thereto.

A further aspect of the present invention is the use of a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, in particular in the subaspects thereto, in more particular in the subaspects emphasized above, as an integral part of the overall structure of compounds, which are suitable to inhibit PDE10, and which have a molecular weight between 200 and 600 daltons.

As exemplary compounds according to this invention may be mentioned any of those compounds individualized and listed as Examples 1 to 28 in the following examples, or a salt, stereoisomer, hydrate or hydrate of a salt thereof.

As further exemplary compounds according to this invention may be mentioned any compound selected from the group consisting of those compounds individualized and listed as Examples 29 to 69 in the following examples, or a salt, stereoisomer, hydrate or hydrate of a salt thereof.

As exemplary compounds according to this invention the following compounds of formula Ic, and the salts, stereoisomers, hydrates or hydrates of the salts thereof,



may be notably mentioned by means of the substituent meanings for R5, R6 and R7 in the following Tables A1, A2, A3 and A4:

Table A1:

- 19 -

Example No.	R5	R6	R7
70.	-CH <sub>3</sub>	-CH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
71.	-CH <sub>3</sub>	-CH <sub>3</sub>	4-carboxy-phenyl
72.	-CH <sub>3</sub>	-CH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
73.	-CH <sub>3</sub>	-CH <sub>3</sub>	4-amino-phenyl
74.	-CH <sub>3</sub>	-CH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
75.	-CH <sub>3</sub>	-CH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
76.	-CH <sub>3</sub>	-CH <sub>3</sub>	4-methylsulphonylamino-phenyl
77.	-CH <sub>3</sub>	-CH <sub>3</sub>	pyridin-4-yl
78.	-CH <sub>3</sub>	-CH <sub>3</sub>	quinolin-4-yl
79.	-CH <sub>3</sub>	-CH <sub>3</sub>	2-methyl-pyridin-4-yl
80.	-CH <sub>3</sub>	-CH <sub>3</sub>	3-methyl-pyridin-4-yl
81.	-CH <sub>3</sub>	-CH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
82.	-CH <sub>3</sub>	-CH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
83.	-CH <sub>3</sub>	-CH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
84.	-CH <sub>3</sub>	-CH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
85.	-CH <sub>3</sub>	-CH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

Table A2:

Example No.	R5	R6	R7
86.	-CN	-CH <sub>3</sub>	4-hydroxy-3,5-dimethylphenyl
87.	-CN	-CH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
88.	-CN	-CH <sub>3</sub>	4-carboxy-phenyl
89.	-CN	-CH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
90.	-CN	-CH <sub>3</sub>	4-amino-phenyl
91.	-CN	-CH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
92.	-CN	-CH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
93.	-CN	-CH <sub>3</sub>	4-methylsulphonylamino-phenyl
94.	-CN	-CH <sub>3</sub>	pyridin-4-yl
95.	-CN	-CH <sub>3</sub>	quinolin-4-yl
96.	-CN	-CH <sub>3</sub>	2-methyl-pyridin-4-yl
97.	-CN	-CH <sub>3</sub>	3-methyl-pyridin-4-yl
98.	-CN	-CH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
99.	-CN	-CH <sub>3</sub>	1-tolylsulphonyl-indol-3-yl
100.	-CN	-CH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
101.	-CN	-CH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
102.	-CN	-CH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
103.	-CN	-CH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

Table A3:

Example No.	R5	R6	R7
104.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-hydroxy-3,5-dimethylphenyl
105.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
106.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-carboxy-phenyl
107.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
108.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-amino-phenyl
109.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
110.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
111.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-methylsulphonylamino-phenyl
112.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	pyridin-4-yl
113.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	quinolin-4-yl
114.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	2-methyl-pyridin-4-yl

- 20 -

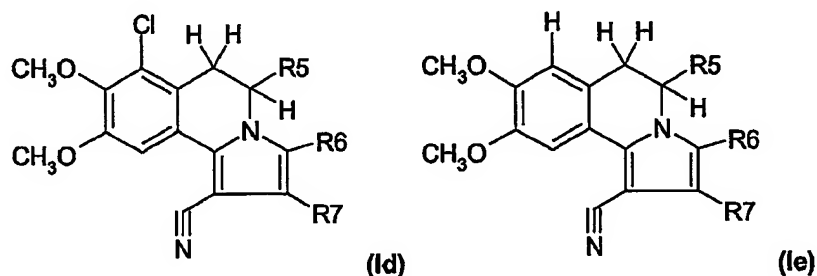
115.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	3-methyl-pyridin-4-yl
116.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
117.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-tolylsulphonyl-indol-3-yl
118.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
119.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
120.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
121.	-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

Table A4:

Example No.	R5	R6	R7
122.	-CN	-CH <sub>3</sub>	4-hydroxy-3,5-dimethylphenyl
123.	-CN	-CH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
124.	-CN	-CH <sub>3</sub>	4-carboxy-phenyl
125.	-CN	-CH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
126.	-CN	-CH <sub>3</sub>	4-amino-phenyl
127.	-CN	-CH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
128.	-CN	-CH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
129.	-CN	-CH <sub>3</sub>	4-methylsulphonylamino-phenyl
130.	-CN	-CH <sub>3</sub>	pyridin-4-yl
131.	-CN	-CH <sub>3</sub>	quinolin-4-yl
132.	-CN	-CH <sub>3</sub>	2-methyl-pyridin-4-yl
133.	-CN	-CH <sub>3</sub>	3-methyl-pyridin-4-yl
134.	-CN	-CH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
135.	-CN	-CH <sub>3</sub>	1-tolylsulphonyl-indol-3-yl
136.	-CN	-CH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
137.	-CN	-CH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
138.	-CN	-CH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
139.	-CN	-CH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

as well as compound 30 and compound 42.

The following compounds of formula Id or Ie, and the salts, stereoisomers, hydrates or hydrates of the salts thereof,



may be also mentioned as exemplary compounds according to this invention by means of the substituent meanings for R5, R6 and R7 in the following Tables B1, B2, B3 and B4:

Table B1:

R5	R6	R7
-CH <sub>3</sub>	-CH <sub>3</sub>	4-hydroxy-3,5-dimethylphenyl

- 21 -

-CH <sub>3</sub>	-CH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
-CH <sub>3</sub>	-CH <sub>3</sub>	4-carboxy-phenyl
-CH <sub>3</sub>	-CH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
-CH <sub>3</sub>	-CH <sub>3</sub>	4-amino-phenyl
-CH <sub>3</sub>	-CH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
-CH <sub>3</sub>	-CH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
-CH <sub>3</sub>	-CH <sub>3</sub>	4-methylsulphonylamino-phenyl
-CH <sub>3</sub>	-CH <sub>3</sub>	pyridin-4-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	quinolin-4-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	2-methyl-pyridin-4-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	3-methyl-pyridin-4-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
-CH <sub>3</sub>	-CH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

- 22 -

Table B2:

R5	R6	R7
-CN	-CH <sub>3</sub>	4-hydroxy-3,5-dimethylphenyl
-CN	-CH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
-CN	-CH <sub>3</sub>	4-carboxy-phenyl
-CN	-CH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
-CN	-CH <sub>3</sub>	4-amino-phenyl
-CN	-CH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
-CN	-CH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
-CN	-CH <sub>3</sub>	4-methylsulphonylamino-phenyl
-CN	-CH <sub>3</sub>	pyridin-4-yl
-CN	-CH <sub>3</sub>	quinolin-4-yl
-CN	-CH <sub>3</sub>	2-methyl-pyridin-4-yl
-CN	-CH <sub>3</sub>	3-methyl-pyridin-4-yl
-CN	-CH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
-CN	-CH <sub>3</sub>	1-tolylsulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

Table B3:

R5	R6	R7
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-hydroxy-3,5-dimethylphenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-carboxy-phenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-amino-phenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	4-methylsulphonylamino-phenyl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	pyridin-4-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	quinolin-4-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	2-methyl-pyridin-4-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	3-methyl-pyridin-4-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-tolylsulphonyl-indol-3-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
-CH <sub>3</sub>	-(CH <sub>2</sub> CH <sub>2</sub> )C(O)OCH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

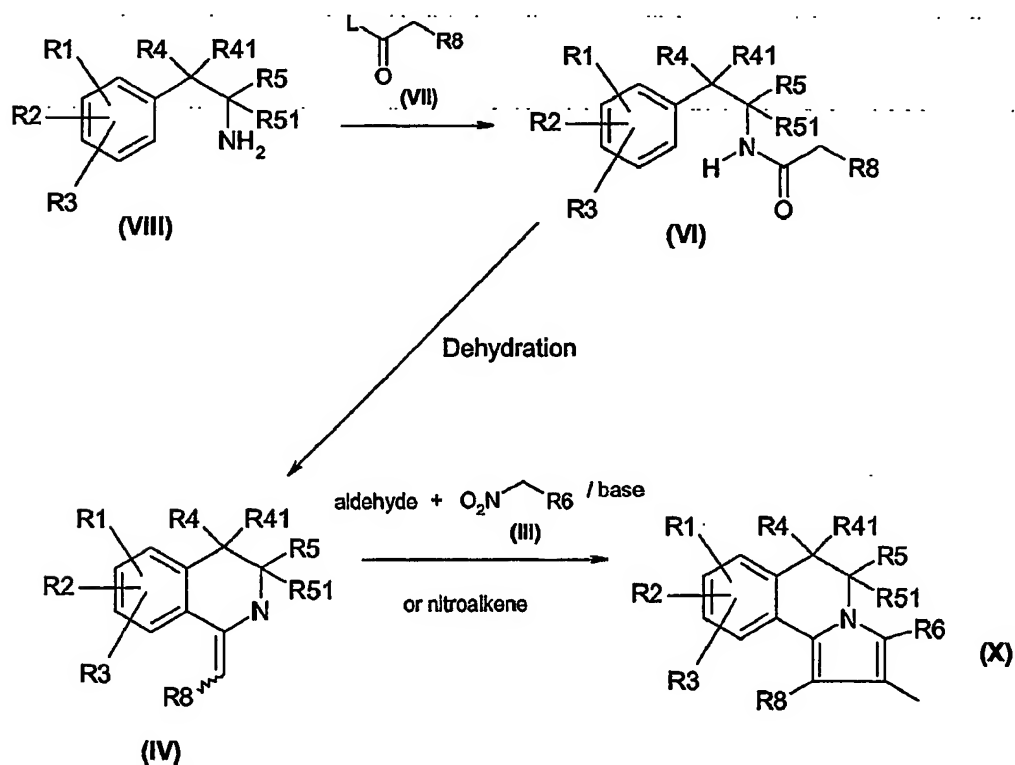
Table B4:

R5	R6	R7
-CN	-CH <sub>3</sub>	4-hydroxy-3,5-dimethylphenyl
-CN	-CH <sub>3</sub>	4-methoxy-3,5-dimethylphenyl
-CN	-CH <sub>3</sub>	4-carboxy-phenyl
-CN	-CH <sub>3</sub>	2-methyl-4-hydroxy-phenyl
-CN	-CH <sub>3</sub>	4-amino-phenyl
-CN	-CH <sub>3</sub>	4-(2H-tetrazol-5-yl)-phenyl
-CN	-CH <sub>3</sub>	4-morpholino-sulphonylamino-phenyl
-CN	-CH <sub>3</sub>	4-methylsulphonylamino-phenyl
-CN	-CH <sub>3</sub>	pyridin-4-yl

- 23 -

-CN	-CH <sub>3</sub>	quinolin-4-yl
-CN	-CH <sub>3</sub>	2-methyl-pyridin-4-yl
-CN	-CH <sub>3</sub>	3-methyl-pyridin-4-yl
-CN	-CH <sub>3</sub>	1-tolylsulphonyl-pyrrol-3-yl
-CN	-CH <sub>3</sub>	1-tolylsulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-phenylsulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-methylsulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-dimethylaminosulphonyl-indol-3-yl
-CN	-CH <sub>3</sub>	1-morpholinosulphonyl-indol-3-yl

The compounds which comprise a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, can be prepared, for example, in an art-known manner, or in a manner described and shown as follows, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116, WO 03/014117 or WO 03/051877, or as described by way of example in the following examples, or analogously or similarly thereto.



As shown in the scheme above, in a first reaction step compounds of formula VIII, in which R1, R2, R3, R4, R41, R5 and R51 have the meanings indicated above, are reacted with compounds of formula VII, in which R8 has the meanings indicated above and L is a suitable leaving group, for example chlorine or an acyloxy radical (e.g. the  $\text{R}_8\text{-CH}_2\text{-C}(\text{O})\text{-O-}$  radical), to give in the presence of a suitable organic or inorganic base corresponding compounds of formula VI.

- 24 -

Alternatively, compounds of formula VI are also accessible from compounds of formula VIII, in which R1, R2, R3, R4, R41, R5 and R51 have the meanings indicated above, and compounds of formula VII, in which R8 has the meanings indicated above and L is hydroxyl, by reaction with amide bond linking reagents known to the person skilled in the art. Exemplary amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, the carbodiimides (e.g. dicyclohexylcarbodiimide or, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts [e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate] and N,N'-carbonyldiimidazole. In the scope of this invention preferred amide bond linking reagents are uronium salts and, particularly, carbodiimides, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

Said reactions are carried out under conditions known to the person skilled in the art or as described exemplarily in the following examples.

As shown in the next step, compounds of the formula IV, in which R1, R2, R3, R4, R41, R5, R51 and R8 have the meanings indicated above, can be obtained by cyclocondensation of corresponding compounds of the formula VI. Said cyclocondensation reaction is carried out in a manner habitual per se to the person skilled in the art or as described by way of example in the following examples, according to Bischler-Napieralski (e.g. as described in J. Chem. Soc., 1956, 4280-4282) in the presence of a suitable condensing or dehydrating agent, such as, for example, polyphosphoric acid, phosphorus pentachloride, phosphorus pentoxide or phosphorus oxychloride, in a suitable inert solvent, e.g. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as acetonitrile, or without further solvent using an excess of condensing agent, at reduced temperature, or at room temperature, or at elevated temperature or at the boiling temperature of the solvent or condensing agent used.

Compounds of formula IV are converted either with suitable aldehydes and compounds of formula III, in which R6 is 1-6C-alkyl or 1-4C-alkyl substituted by 1-4C-alkoxycarbonyl, or with suitable nitroalkenes, optionally in an one pot synthesis and suitably in the presence of an inorganic or organic base (in particular a cyclic amine, e.g. piperidine) into corresponding compounds which comprise a structure-element of the formula X, Xa or Xb. Said conversion can be carried out as known to the skilled person or as described in the following examples or analogously or similarly thereto.

Said suitable aldehydes, nitroalkenes and compounds of formulae VIII, VII and III are commercially available or can be obtained in a manner known to the skilled person from his/her expert knowledge and/or from literature.

Suitable nitroalkenes are known or are accessible by reaction of suitable aldehydes with nitro compounds of formula III in the presence of a suitable organic or inorganic base in a manner customary per se to the skilled person.



- 25 -

Compounds obtained can be converted into further compounds, which comprise a structure-element of the formula X, Xa or Xb, by methods known to one of ordinary skill in the art. More specifically, for example, from compounds, in which

- a.) R61 are an ester group, the corresponding acids can be obtained by acidic or, particularly, alkaline hydrolysis;
- b.) R6 is 1-4C-alkyl, particularly methyl, the corresponding halogenated, preferably chlorinated, groups can be obtained by halogenation reaction, particularly by reaction with a chlorination reagent such as sulfuryl chloride, thionyl chloride or N-chlorosuccinimide;
- c.) R6 is 1-4C-alkyl substituted by halogen, the corresponding derivatized 1-4C-alkyl radicals substituted by 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612 can be obtained by nucleophilic substitution reactions with suitable nucleophiles;
- d.) R6 is 1-4C-alkyl substituted by hydroxyl, the corresponding derivatized 1-4C-alkyl radicals substituted by 1-4C-alkoxycarbonyl can be obtained by oxidation and esterification reactions under suitable conditions;
- e.) R6 is methyl, the corresponding oxidized forms thereof (e.g. the hydroxymethyl or formyl radicals) can be obtained stepwise or directly by selective oxidation reactions (e.g. with the aid of manganese dioxide to obtain the formyl radicals);
- f.) R6 is formyl, the corresponding aminated compounds can be obtained by reductive amination reaction;
- g.) R6 is hydroxymethyl, the corresponding fluorine compounds can be obtained by fluorination reaction;
- h.) R6 is methyl, the corresponding amino compounds can be obtained by nitration reaction and subsequential reduction of the nitro compounds obtained.

The methods mentioned under a.) to h.) are expediently carried out analogously to the methods known to the person skilled in the art or as described by way of example in the following examples.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3<sup>rd</sup> Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

The isolation and purification of the compounds according to the invention, i.e. the compounds with the structure-element of the formula X, Xa or Xb, is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column

- 26 -

chromatography on suitable support material.

The compounds according to the present invention include suitable salt forms. Suitable salts for compounds according to the invention - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds according to the invention as well as all solvates and in particular all hydrates of the salts of the compounds according to the invention.

- 27 -

Depending on substitution the compounds according to the present invention can be chiral compounds having, for example, chiral centers and/or chiral axes due to hindered rotation about single bonds. The invention therefore includes all conceivable pure diastereomers and pure enantiomers and mixtures thereof in any mixing ratio including the racemates. The diastereomer mixtures can be separated into the individual isomers by chromatographic processes. The enantiomers can be separated in a known manner (e.g. by chromatographic processes on chiral phases or by resolution).

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes compounds according to the invention. All these other possible synthesis routes are also part of this invention.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, variations and adaptations to the described invention can be made on the base of the disclosure (e.g. the explicite, implicate or inherent disclosure) of the present invention without departing from the spirit and scope of this invention.

The following examples serve to illustrate the invention in greater detail without restricting it. Likewise, further compounds which comprise a structure-element of the formula X, Xa or Xb, whose preparation is not explicitly described, can also be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples, m.p. stands for melting point, h for hour(s), min for minutes, conc. for concentrated, satd. for saturated, MS for mass spectrum, M for molecular ion.

Unless otherwise noted, if the exemplary compounds mentioned expressis verbis herein contain a chirality center, they are described illustratively as racemic mixtures herein, without restricting this invention thereto.

The compounds mentioned in the examples as well as their salts and stereoisomers are a particular interesting subject of the invention.

### Examples

#### **Final products**

1. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5,5-trimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester

Analogously to a procedure described by Meyer in Liebigs Ann. Chem. 1981, 9, 1534-1544, (6,7-dimethoxy-3,3-dimethyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester (compound A7) is reacted with nitro ethane and 4-hydroxy-3,5-dimethyl benzaldehyde to afford the title compound.

MS (M+H) = 464.1; m.p. = 210 – 213 °C

The following examples (Examples 2-20) can be prepared in analogy to example 1 using the appropriate starting compound selected from the group consisting of the compounds A1 to A9. All aldehydes used are commercially available or can be prepared in analogy to published procedures. If nitro propane or 4-nitro butyric acid methyl ester is used instead of nitroethane, 3-ethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines and 3-methoxycarbonyl-ethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines (e.g. 3-(8,9-dimethoxy-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-3-yl)propionic methyl esters), respectively are obtained.

2. 8,9-Dimethoxy-3,5,5-trimethyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 510.4; m.p. = 52 – 56 °C
3. 2-[3-(4-Chloro-phenoxy)-phenyl]-8,9-dimethoxy-3,5,5-trimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 546.2; m.p. = 61 – 64 °C
4. 2-(3-Dimethylamino-phenyl)-8,9-dimethoxy-3,5,5-trimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 463.1; m.p. = 101 – 102 °C
5. (5RS)- (4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 450.2; m.p. = 158 – 161 °C
6. (5RS)-5-Ethyl-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 464.1; m.p. = 164 – 166 °C

- 29 -

7. (5RS)-2-Chlorophenyl-5-ethyl-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 454.2; m.p. = 121 – 124 °C
8. (4aRS,8aRS)-cis-2-(4-hydroxy-3,5-dimethyl-phenyl)-10,11-dimethoxy-3-methyl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester  
MS (M+H) = 490.2; m.p. = 186 – 192 °C
9. (5RS)-3-Ethyl-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-5-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 464.1; m.p. = 188 – 190 °C
10. (5RS)-8,9-Dimethoxy-3,5-dimethyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 496.0; m.p. = 116 – 118 °C
11. (5RS)-8,9-Dimethoxy-3,5-dimethyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 456.1; m.p. = 184 °C
12. (4aRS,8aRS)-cis-10,11-Dimethoxy-3-methyl-2-naphthalen-1-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester  
MS (M+H) = 496.1; m.p. = 189 – 191 °C
13. (4aRS,8aRS)-cis-10,11-Dimethoxy-3-methyl-2-quinolin-4-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester  
MS (M+H) = 497.3; m.p. = 153 – 157 °C
14. (4aR,8aR)-10,11-Dimethoxy-3-methyl-2-quinolin-4-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester  
MS (M+H) = 497.3; oil
15. (4aR,8aR)-10,11-Dimethoxy-3-methyl-2-naphthalen-1-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester  
MS (M+H) = 496.1; m.p. = 212 – 216 °C
16. (4aR,8aR)-2-(4-Hydroxy-3,5-dimethyl-phenyl)-10,11-dimethoxy-3-methyl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester  
MS (M+H) = 490.2; m.p. = 203 – 206 °C

- 30 -

17. (5RS)-5-Ethyl-8,9-dimethoxy-3-methyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 470.1; oil
18. (5RS)-2-(4-Hydroxy-3,5-dimethyl-phenyl)-7,8,9-trimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 480.0; m.p. = 144 °C
19. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1,5-dicarboxylic acid 1-ethyl 5-methyl ester  
MS (M+H) = 494.1; m.p. = 92 – 97 °C
20. (5RS)-8,9-Dimethoxy-3-(2-methoxycarbonyl-ethyl)-5-methyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 528.1; m.p. = 56 – 59 °C
21. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

Analogously to the procedure described for Example 1, (6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetonitrile (compound A8) is reacted with nitro ethane and 4-hydroxy-3,5-dimethyl benzaldehyde to afford 2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile as a colorless solid of m.p. 285 – 287 °C. The mass spectrum shows the molecular peak M+H at 388.5 Da.

The following examples (Nos. 22-28) can be prepared in analogy to example 21 using the appropriate starting compound A8 or A9. All aldehydes used are commercially available or can be prepared in analogy to published procedures. If nitro propane or 4-nitro butyric acid methyl ester is used instead of nitroethane, 3-ethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines and 3-methoxycarbonylethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines, respectively are obtained.

22. 8,9-Dimethoxy-3-methyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 395.2; m.p. = 226 – 229 °C
23. 8,9-Dimethoxy-3-methyl-2-quinolin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 396.3; m.p. = 239 – 243 °C
24. 2-(1H-Indol-3-yl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 384.3; m.p. = 304 – 307 °C

- 31 -

25. 2-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 473.1; m.p. = 250 – 252 °C
26. 8,9-Dimethoxy-3,5-dimethyl-2-pyridin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 360.3; m.p. = 253 – 254 °C
27. 3-[1-Cyano-2-(4-hydroxy-3,5-dimethyl)-8,9-dimethoxy-5-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-3-yl]-propionic acid methyl ester  
MS (M+H) = 475.2; m.p. = 208 – 209 °C
28. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 403.2; m.p. = 268 – 270 °C

The following examples (Nos. 29-59) can be prepared in analogy to example 21 using the appropriate starting compound, which can be prepared in an art-known manner, or analogously or similarly as described for A8 or A9. All aldehydes used are commercially available or can be prepared in analogy to published procedures. If nitro propane or 4-nitro butyric acid methyl ester is used instead of nitroethane, 3-ethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines and 3-methoxycarbonyl-ethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines, respectively are obtained.

29. 3-(1-Cyano-8,9-dimethoxy-2-pyridin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-3-yl)-propionic acid methyl ester  
MS (M+H) = 417.9; m.p. = 191 – 193 °C
30. 7-Fluoro-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 421.2; m.p. = 166 – 168 °C
31. 3-(1-Cyano-8,9-dimethoxy-2-quinolin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-3-yl)-propionic acid methyl ester  
MS (M+H) = 467.9; m.p. = 232 – 234 °C
32. 3-[1-Cyano-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-3-yl]-propionic acid methyl ester  
MS (M+H) = 461.0; m.p. = 217 – 219 °C
33. 8,9-Dimethoxy-2-(4-methoxy-3,5-dimethyl-phenyl)-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

- 32 -

MS (M+H) = 417.3;

34. 2-(1H-Indol-5-yl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 384.3;

35. 8,9-Dimethoxy-2-(4-methoxy-3,5-dimethyl-phenyl)-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 403.3;

36. 2-(1-Benzyl-2,3-dihydro-1H-indol-5-yl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 476.1;

37. 8,9-Dimethoxy-3,5-dimethyl-2-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 502.1;

38. 8,9-Dimethoxy-3,5-dimethyl-2-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 569.0;

39. 2-(1-Benzenesulfonyl-1H-indol-3-yl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 537.7;

40. 2-(1-Methanesulfonyl-1H-indol-3-yl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 475.8; m.p. = 219 – 221 °C

41. 8,9-Dimethoxy-3,5-dimethyl-2-(1-oxy-pyridin-4-yl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 375.8; m.p. = 279 – 282 °C

42. 7-Fluoro-8,9-dimethoxy-3,5-dimethyl-2-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 587.0;

43. 2-(2,3-Dihydro-1H-indol-5-yl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile

MS (M+H) = 386.3;



- 33 -

44. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-5-methyl-3-morpholin-4-ylmethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
m.p. = 228 – 230 °C
45. 8,9-Dimethoxy-3,5-dimethyl-2-(2-methyl-pyridin-4-yl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 374.2; m.p. = 187 – 189 °C
46. 8,9-Dimethoxy-3,5-dimethyl-2-(4-nitro-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 403.7; m.p. = 206 – 207 °C
47. 4-(1-Cyano-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-benzoic acid  
MS (M+H) = 402.7; m.p. = 287 – 289 °C
48. 2-(4-Amino-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 374.1; m.p. = 237 – 239 °C
49. 8,9-Dimethoxy-3,5-dimethyl-2-(3-methyl-pyridin-4-yl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 374.5; m.p. = 232 – 233 °C
50. 4-(1-Cyano-8-ethoxy-9-methoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-benzoic acid  
MS (M+H) = 417.2; m.p. = 274 – 277 °C
51. 2-(4-Hydroxy-2-methyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 389.1; m.p. = 228 – 230 °C
52. 4-(1-Cyano-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-benzamide  
m.p. = 228 – 230 °C
53. 8-Ethoxy-2-(4-hydroxy-3,5-dimethyl-phenyl)-9-methoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 417.2; m.p. = 232 – 234 °C

- 34 -

54. 3-(1-Cyano-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-indole-1-sulfonic acid dimethylamide  
MS (M+H) = 505.2; m.p. = 236 – 237 °C
55. 8,9-Dimethoxy-3,5-dimethyl-2-(2-methyl-1-oxy-pyridin-4-yl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 390.1; m.p. = 265 – 268 °C
56. 8,9-Dimethoxy-3,5-dimethyl-2-[1-(morpholine-4-sulfonyl)-1H-indol-3-yl]-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 574.1; m.p. = 210 – 212 °C
57. 8,9-Dimethoxy-3,5-dimethyl-2-[4-(2H-tetrazol-5-yl)-phenyl]-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile  
MS (M+H) = 427.2; m.p. = 204 – 207 °C
58. Morpholine-4-sulfonic acid [4-(1-cyano-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-phenyl]-amide  
MS (M+H) = 523.1; m.p. = 223 – 225 °C
59. N-[4-(1-Cyano-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-phenyl]-methanesulfonamide  
MS (M+H) = 452.1; m.p. = 257 – 259 °C

The following examples (Examples 60-67) can be prepared in analogy to example 1 using the appropriate starting compound, which can be prepared in an art-known manner, or analogously or similarly as described for compounds A1 to A9. All aldehydes used are commercially available or can be prepared in analogy to published procedures. If nitro propane or 4-nitro butyric acid methyl ester is used instead of nitroethane, 3-ethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines and 3-methoxycarbonyl-ethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolines, respectively are obtained.

60. 5-Ethyl-2-(2-fluoro-3,4-dimethoxy-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 498.1;
61. 7-Chloro-8,9-dimethoxy-3,5-dimethyl-2-pyridin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 441.3;

- 35 -

62. 7-Chloro-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 484.0;
63. 7,8,9-Trimethoxy-3,5-dimethyl-2-pyridin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 437.3;
64. 8,9-Dimethoxy-3-(2-methoxycarbonyl-ethyl)-5-methyl-2-quinolin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 529.3;
65. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid methyl ester  
MS (M+H) = 435.9; m.p. = 177 – 179 °C
66. 8,9-Dimethoxy-3,5-dimethyl-2-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid methyl ester  
MS (M+H) = 584.9; m.p. = 177 – 179 °C
67. 5-Cyano-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 461.0;
68. 4-(8,9-Dimethoxy-1,3-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-2,6-dimethyl-phenol  
MS (M+H) = 377.9; m.p. = 183 – 185 °C  
The title compound can be obtained via an analogous synthesis route as described for the Examples herein.
69. 8,9-Dimethoxy-3-(2-methoxycarbonyl-ethyl)-5-methyl-2-quinolin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester  
MS (M+H) = 407.9; m.p. = 176 – 177 °C  
The title compound can be obtained from the corresponding ester compound, which is accessible analogously as described in Example 1 herein, by art-known saponification reaction.

Exemplary compounds of formula Ic mentioned as Examples 70-139 in Tables A1 to A4 can be prepared analogously or similarly to the described examples.

- 36 -

Exemplary compounds of formulae Id or Ie can be also prepared analogously or similarly to the described examples.

#### Starting compounds

**A1** (3RS)-(6,7-Dimethoxy-3-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester  
The title compound can be obtained by a Bischler-Napieralski reaction (Ber. 1893, 26, 1903) using N-[2-[4-methoxy-3-(2-methoxy-ethoxy)-phenyl]-ethyl]-malonamic acid ethyl ester (compound B1) as the starting material.

The following 3,4-Dihydro-1(2H)-isoquinolinyldene-derivatives A2 to A9 and also further relevant, non-explicitly described similar compounds can be prepared according to an analogous procedure using the appropriate starting compound B2 to B8, or an appropriate analogous compound:

- A2** (3RS)-(3-Ethyl-6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester  
**A3** ((4aR,10bR)-8,9-Dimethoxy-1,3,4,4a,5,10b-hexahydro-2H-phenanthridin-6-ylidene)-acetic acid ethyl ester  
**A4** ((4aRS,10bRS)-cis-8,9-Dimethoxy-1,3,4,4a,5,10b-hexahydro-2H-phenanthridin-6-ylidene)-acetic acid ethyl ester  
**A5** 1-Ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester  
**A6** (3RS)-(5,6,7-Trimethoxy-3-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester  
**A7** (6,7-Dimethoxy-3,3-dimethyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester  
The compound A19 is commercially available.  
**A8** (6,7-Dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetonitrile  
The compound A8 can be prepared analogously to the above-described synthesis of compound A1 using the starting compound B7.  
**A9** (6,7-Dimethoxy-3-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetonitrile  
The compound A9 can be prepared analogously to the above-described synthesis of compound A1 using the starting compound B8.

**B1** N-[(RS)-2-(3,4-Dimethoxy-phenyl)-1-methyl-ethyl]-malonamic acid ethyl ester  
The title compound can be prepared by a reaction of (RS)-2-(3,4-Dimethoxy-phenyl)-1-methyl-ethylamine (compound C1) with ethyl maloyl chloride in analogy to procedures in the literature (e.g. Benovsky et al., Tetrahedron Lett. 1997, 38, 8475-8478).

The following amides B2 to B8 can be synthesized according an analogous procedure:

- B2** N-[(RS)-1-(3,4-Dimethoxy-benzyl)-propyl]-malonamic acid ethyl ester  
**B3** N-[(1R,2R)-2-(3,4-Dimethoxy-phenyl)-cyclohexyl]-malonamic acid ethyl ester

- 37 -

- B4 N-[(1RS,2RS)-cis-2-(3,4-Dimethoxy-phenyl)-cyclohexyl]-malonamic acid ethyl ester  
B5 3-(3,4-Dimethoxy-phenyl)-2-(2-ethoxycarbonyl-ethanoylamino)-propionic acid methyl ester  
B6 N-[(RS)-1-Methyl-2-(2,3,4-trimethoxy-phenyl)-ethyl]malonamic acid ethyl ester

B7 2-Cyano-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide

A solution of 10.0 g (55.1 mmol) of 2-(3,4-dimethoxy-phenyl)-ethylamine and 9.36 g (82.7 mmol) of ethyl cyano acetate is stirred at 100 °C for 15 h. The mixture is cooled to room temperature. The precipitate is filtered off and recrystallized from ethanol. 9.44 g (38.0 mmol, 60 %) of 2-cyano-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide are obtained as a beige solid.

MS (M+H) = 249.0, m.p. = 113-115 °C.

B8 2-Cyano-N-[2-(3,4-dimethoxy-phenyl)-1-methyl-ethyl]-acetamide

Compound B8 can be prepared analogously to the synthesis of compound B7.

The appropriate starting compounds for the preparation of the compounds B1 to B8 are commercially available, or can be prepared as described below in the synthesis of the compound C1 or analogously or similarly thereto, or can be obtained in analogy to published procedures, e.g. the substituted 2-phenethyl amines can be prepared starting from the corresponding benzaldehydes (see also Shepard et al., J. Org. Chem. 1952, 17, 568).

C1 (RS)-2-(3,4-Dimethoxy-phenyl)-1-methyl-ethylamine

The title compound can be prepared by a sequence described by Shepard et al. in J. Org. Chem. 1952, 17, 568.

**Commercial utility****Commercial applicability**

Intracellular levels of the second messengers cAMP and cGMP are regulated by both their rates of synthesis by cyclases and their hydrolysis by phosphodiesterases. Of the 11 phosphodiesterase (PDE) isoenzymes which are presently known, PDE10 was described for the first time in 1999 (Soderling SH, Bayuga SJ, Beavo JA. Isolation and characterization of a dual-substrate phosphodiesterase gene family: PDE10A. *Proc Natl Acad Sci U S A*. 1999 Jun 8;96(12):7071-6; Fujishige K, Kotera J, Michibata H, Yuasa K, Takebayashi S, Okumura K, Omori K. Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A). *J Biol Chem*. 1999 Jun 25;274(26):18438-45; Loughney K, Snyder PB, Uher L, Rosman GJ, Ferguson K, Florio VA. Isolation and characterization of PDE10A, a novel human 3', 5'-cyclic nucleotide phosphodiesterase. *Gene*. 1999 Jun 24;234(1):109-17). The first gene of this new PDE subfamily was designated PDE10A and the first splice variant was described as PDE10A1, according to the current nomenclature. Due to alternative splicing, other splice variants of PDE10A exist and have been described in the subsequent years (Kotera J, Fujishige K, Yuasa K, Omori K. Characterization and phosphorylation of PDE10A2, a novel alternative splice variant of human phosphodiesterase that hydrolyzes cAMP and cGMP. *Biochem Biophys Res Commun*. 1999 Aug 11;261(3):551-7; Fujishige K, Kotera J, Omori K. Striatum- and testis-specific phosphodiesterase PDE10A Isolation and characterization of a rat PDE10A. *Eur J Biochem*. 1999 Dec;266(3):1118-27; Fujishige K, Kotera J, Yuasa K, Omori K. The human phosphodiesterase PDE10A gene genomic organization and evolutionary relatedness with other PDEs containing GAF domains. *Eur J Biochem*. 2000 Oct;267(19):5943-51). PDE10A has been described as a cyclic nucleotide phosphodiesterase exhibiting properties of a cAMP PDE and a cAMP-inhibited cGMP PDE.

Individual representatives of the PDE10 isoenzyme are characterized by being particularly prominently expressed in specific areas of the brain (striatum, putamen, caudate nucleus, cerebellum, thalamus), in testis, in the thyroid gland, in the pituitary gland, in kidney and in placenta. Increased expression levels in a broad variety of tumor cell lines and tissues, namely of the lung, breast, pancreas, brain, prostate and ovaries indicates that PDE10 may play an important role in tumor cell growth and/or survival under conditions of elevated cAMP and/or cGMP generation. Increased expression levels and activities of PDE10A have been also found in testis suggesting that PDE10A may contribute to spermatogenesis (Fujishige K et al., *Eur J Biochem*. 1999, 266:1118-27). Certain PDE inhibitors, namely e.g. PDE3 or PDE11A inhibitors, are known to augment glucose-induced insulin secretion and thus may be useful for treating diabetes (see e.g. WO 03/077949).

The use of the structure-element according to the present invention as an integral part of the overall structure of compounds, which inhibit PDE10, can be commercially utilized to provide (i.e. e.g. to

- 39 -

design and to manufacture) compounds according to this invention having valuable pharmacological and pharmaceutical properties.

Accordingly, the compounds according to the invention, i.e. compounds containing a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A or in the subaspects thereto, have miscellaneous valuable pharmacological properties which make them commercially utilizable.

Thus, for example, the compounds according to this invention are PDE inhibitors.

Yet thus, for example, the compounds according to the invention are potent PDE10 inhibitors, some of which are apparently selective (by >100 fold) among other PDE isoenzymes, whereby these selective compounds are particularly preferred in the context of the present invention. The compounds according to the invention therefore can be employed as therapeutic agents for the treatment or prophylaxis of diseases in human and veterinary medicine.

Due to their potent and selective PDE10 inhibitory activity, the compounds according to the present invention may be, in a first facet of the present invention, of potential value in treating disorders of the central nervous system, in particular neurologic and psychiatric disorders, for example those mentioned in EP 1250923 and/or, in more particular, psychotic disorders, anxiety disorders, mood disorders or episodes, drug addiction, movement disorders or disorders comprising deficient cognition as a symptom (e.g. dementia, Parkinson's disease or Alzheimer's disease).

Furthermore, the compounds according to the present invention may be, in a second facet of the present invention, of potential value in treating certain disorders of the central nervous system, in particular neurologic and psychiatric disorders, for example those mentioned generically, specifically or exemplarily in EP 1250923, US 2003/0008806 and/or US 2003/0018047, such as, for example, anxiety or psychotic disorders, movement disorders, obsessive/compulsive disorders, drug addictions, cognition deficiency disorders, mood disorders or mood episodes, or neurodegenerative disorders.

In this context, examples of anxiety disorders, which may be treated by the compounds according to the present invention, include, without being limited thereto, panic disorder, agoraphobia, a specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, or generalized anxiety disorder.

Examples of psychotic disorders, which may be treated by the compounds according to the present invention, include, without being limited thereto, schizophrenia (for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type), schizophreniform disorder, schizoaffective disorder (for example of the delusional type or the depressive type), delusional disorder, substance-induced psychotic disorder (for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine), personality disorder of the paranoid type, or personality disorder of the schizoid type.

- 40 -

Examples of movement disorders, which may be treated by the compounds according to the present invention, include, without being limited thereto, Parkinson's disease, or restless leg syndrome.

Examples of obsessive/compulsive disorders, which may be treated by the compounds according to the present invention, include, without being limited thereto, Tourette's syndrome, or other tic disorders.

Examples of drug addictions, which may be treated by the compounds according to the present invention, include, without being limited thereto, an alcohol, amphetamine, cocaine, or opiate addiction.

Examples of cognition deficiency disorders, which may be treated by the compounds according to the present invention, include, without being limited thereto, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia, delirium, amnesic disorder, post-traumatic stress disorder, mental retardation, a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression, attention-deficit/hyperactivity disorder, or age-related cognitive decline.

Examples of mood disorders or mood episodes, which may be treated by the compounds according to the present invention, include, without being limited thereto, a major depressive episode of the mild, moderate or severe type, a manic or mixed mood episode, a hypomanic mood episode, a depressive episode with a typical features, a depressive episode with melancholic features, a depressive episode with catatonic features, a mood episode with postpartum onset, post-stroke depression, major depressive disorder, dysthymic disorder, minor depressive disorder, premenstrual dysphoric disorder, post-psychotic depressive disorder of schizophrenia, a major depressive disorder superimposed on a psychotic disorder such as delusional disorder or schizophrenia, a bipolar disorder (for example bipolar I disorder, bipolar II disorder), or cyclothymic disorder.

Examples of neurodegenerative disorders, which may be treated by the compounds according to the present invention, include, without being limited thereto, Parkinson's disease, Huntington's disease, dementia (for example Alzheimer's disease, multi-infarct dementia, AIDS-related dementia, or Frontotemporal Dementia), neurodegeneration associated with cerebral trauma, neurodegeneration associated with stroke, neurodegeneration associated with cerebral infarct, hypoglycemia-induced neurodegeneration, neurodegeneration associated with epileptic seizure, neurodegeneration associated with neurotoxin poisoning, or multi-system atrophy.

Yet in this context, the compounds according to the present invention may be of potential value for treating diseases or conditions, in which abnormal function of the basal ganglia has been implicated. Thus, abnormal function of the basal ganglia may be involved in dysregulated motoric, appetitive



- 41 -

and/or cognitive processes. Exemplary neuropsychiatric conditions, in which abnormal function of the basal ganglia has been implicated, are mentioned e.g. in EP 1250923, US 2003/0008806 and/or US 2003/0018047, such as e.g. psychosis, attention-deficit/hyperactivity disorder (ADHD) and related attentional disorders, depression, obsessive compulsive disorders including Tourette's syndrome and other tic disorders, and substance abuse. Several neurological disorders including Parkinson's disease, restless leg syndrome and Huntington's disease can be also linked to basal ganglia dysfunction.

Still yet in this context, the compounds according to the present invention may be of potential value for improving cognition, powers of concentration, learning skills or hypermesia, in particular if the disorder is a symptom of dementia.

Yet furthermore, the compounds according to the present invention may be, in a third facet of the present invention, of potential value for regulating fertility in men, e.g. via reducing spermatogenesis and/or via reducing sperm motility.

Still yet furthermore, the compounds according to the present invention may be, in a fourth facet of the present invention, of potential value for treating diabetes, such as, for example, type II diabetes, e.g. via augmenting glucose-induced insulin secretion.

A special interest in the compounds according to the present invention lies in their use in therapy of schizophrenia.

Another special interest in the compounds according to the present invention lies in their use in the therapy of psychotic disorders.

Another special interest in the compounds according to the present invention lies in their use in the therapy of drug addictions.

The invention further relates to a method for treating mammals, including humans, which/who are suffering from one of the abovementioned diseases and/or disorders. The method is characterized by the fact that a pharmacologically active and therapeutically effective and tolerated quantity of one or more of the compounds according to the invention is administered to the affected mammal.

The invention further relates to a method for treating mammals, in particular humans, which/who are suffering from one of the abovementioned diseases and/or disorders comprising the step of administering to said ill mammal a pharmaceutically acceptable composition according to the present invention.

- 42 -

The invention further relates to the compounds according to the invention for use in the treatment or prophylaxis of diseases, in particular said diseases and/or disorders.

The invention likewise relates to the use of the compounds according to the invention in the manufacture of pharmaceutical compositions which are employed for the treatment of said diseases or disorders.

The invention further relates to pharmaceutical compositions for the treatment or prophylaxis of the said diseases and/or disorders, which pharmaceutical compositions comprise one or more of the compounds according to the invention.

The present invention further relates to pharmaceutical compositions comprising one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or diluent.

The present invention further relates to combinations comprising one or more of the compounds according to this invention and pharmaceutically acceptable auxiliaries, excipients or vehicles, e.g. for use in the treatment of those conditions mentioned above.

The present invention further relates to the use of the compounds according to this invention for the production of pharmaceutical compositions which can be used in therapy of disorders responsive to inhibiting of PDE, such as e.g. PDE10.

The present invention further relates to compounds according to this invention having PDE, particularly PDE10, inhibiting properties.

The present invention further relates to pharmaceutical combinations or compositions according to this invention having PDE10 inhibiting properties.

The invention further relates to the use of a pharmaceutical composition comprising one or more of the compounds according to this invention as sole active ingredient(s) and a pharmaceutically acceptable carrier or diluent in the manufacture of pharmaceutical products for therapy, amelioration or prophylaxis of the illnesses, diseases, disorders or conditions mentioned above.

In addition, the present invention further relates to a method for regulating fertility in a mammal, including human, comprising administering one or more compounds according to this invention to said mammal in need thereof.

In further addition, the present invention further relates to the use of the compounds according to this invention for inhibiting spermatogenesis and/or inhibiting sperm motility in a mammal, including human.

- 43 -

In yet further addition, the present invention further relates to the use of the compounds according to this invention for regulating fertility in a mammal, including human.

The invention furthermore relates to a commercial product which consists of a customary secondary packaging means, a primary packaging means (for example an ampoule or a blister pack) which contains a pharmaceutical composition, and, if desired, a patient information leaflet, with the pharmaceutical composition exhibiting an antagonistic effect toward type 10 cyclic nucleotide phosphodiesterases (PDE10) and leading to the attenuation of the symptoms of diseases and/or disorders which are associated with type 10 cyclic nucleotide phosphodiesterases, and with reference being made, on the secondary packaging means and/or on the patient information leaflet of the commercial product, to the suitability of the pharmaceutical composition for use in the prophylaxis or treatment of diseases and/or disorders which are associated with type 10 cyclic nucleotide phosphodiesterases, and with the pharmaceutical composition comprising one or more compounds according to this invention. The secondary packaging means, the primary packaging means containing the pharmaceutical composition and the patient information leaflet otherwise correspond to what the skilled person would regard as being the standard for drugs of this nature.

The pharmaceutical compositions according to this invention are produced using methods with which the skilled person is familiar. When employed in pharmaceutical compositions, the compounds according to the invention (= active compounds) are either used as such or, preferably, in combination with suitable pharmaceutical auxiliaries or formulating agents, for example in the form of tablets, coated (e.g. sugar-coated) tablets, capsules, caplets, suppositories, patches (e.g. as TTS), plasters, emulsions, suspensions, gels or solutions, with the content of active compound advantageously being between 0.1 and 95%, and where, by the appropriate choice of the auxiliaries, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar, on the basis of his/her knowledge, with auxiliaries, vehicles, formulating agents, carriers, diluents, adjuvants or excipients which are suitable to be used for the desired pharmaceutical formulations, preparations or compositions. Beside solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrines).

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, inhalative, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral or intravenous delivery are preferred.

- 44 -

The pharmaceutical compositions according to the invention are prepared by processes known per se. For producing the drugs, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliary substances and further processed into suitable medicinal formulations. Suitable medicinal formulations which may be mentioned by way of example are powders, emulsions, suspensions, sprays, oils, ointments, greasy ointments, creams, pastes, gels and solutions.

The required dosage of the active compounds according to this invention can vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to about 100 mg/kg body weight, conveniently administered, for example, in divided doses up to four times a day or in retard form.

The optimal dose and manner of administration of the active compounds necessary in each case can easily be determined by any person skilled in the art on the basis of his/her expert knowledge.

Depending upon the particular disease, to be treated or prevented, additional therapeutic active agents, which are normally administered to treat or prevent that disease, may optionally be coadministered separately, simultaneously, sequentially or chronologically staggered with the compounds according to this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease are known as appropriate for the disease being treated.

The person skilled in the art is aware on the base of his/her expert knowledge of the total daily dosage(s) of the additional therapeutic agent(s) coadministered. Said total daily dosage(s) can vary within a wide range.

### **Biological Investigations**

Methods to determine the activity and selectivity of a phosphodiesterase inhibitor are known to the person skilled in the art. In this connection it may be mentioned, for example, the methods described by Thompson et al. (Adv Cycl Nucl Res 10: 69-92, 1979), Giembycz et al. (Br J Pharmacol 118: 1945-1958, 1996) and the phosphodiesterase scintillation proximity assay of Amersham Pharmacia Biotech.

#### **Inhibiting the activity of PDE10A**

The PDE10A is cloned into pCR2.1-Topo (Invitrogen) via PCR from human whole brain cDNA using primers OZ 353 (5'- ACCATGTTGACAGATGAAAAAGTGAAGGC -3') and OZ 317 (5'- TCAATCTTCAGATGCAGCTGCC -3'). The ORF encoding for the PDE10A is cut with EcoRV and BamHI and subcloned into SmaI and Bgl II of the expression vector pBP9 (Clontech). The encoded protein represents the PDE10A1 (GenBank Acc.-# AB020593) truncated at its N-terminus at aa 14.

The recombinant baculoviruses are prepared by means of homologous recombination in Sf9 insect cells. The expression plasmids are cotransfected with Bac-N-Blue (Invitrogen) or Baculo-Gold DNA (Pharmingen) using a standard protocol (Pharmingen). Wildtype virus-free recombinant virus supernatants are selected using plaque assay methods. After that, high-titre virus supernatants are prepared by amplifying 3 times. PDE10A1 is expressed in Sf21 cells by infecting  $2 \times 10^6$  cells/ml with an MOI (multiplicity of infection) between 1 and 10 in serum-free SF900 medium (Life Technologies, Paisley, UK). Cells are cultured at 28°C, typically for 48 hours, after which they are pelleted for 5-10 min at 1000 g and 4°C. In spinner flasks, cells are cultured at a rotational speed of 75 rpm. The Sf21 insect cells are resuspended, at a concentration of approx.  $1 \times 10^7$  cells/ml, in ice-cold (4°C) homogenization buffer (20 mM Tris, pH 8.2, containing the following additions: 140 mM NaCl, 3.8 mM KCl, 1 mM EGTA, 1 mM  $MgCl_2$ , 10 mM  $\beta$ -mercaptoethanol, 2 mM benzamidine, 0.4 mM Pefabloc, 10  $\mu$ M leupeptin, 10  $\mu$ M pepstatin A, 5  $\mu$ M trypsin inhibitor) and disrupted by ultrasonication on ice. The homogenate is then centrifuged for 10 min at 1000 g (4 °C) and the supernatant is stored at -80 °C until subsequent use (see below). The protein content is determined by the Bradford method (BioRad, Munich) using BSA as the standard.

The PDE10A activity is inhibited by said compounds in a modified SPA (scintillation proximity assay) test, supplied by Amersham Pharmacia Biotech (see procedural instructions "Phosphodiesterase [3H]cAMP SPA enzyme assay, code TRKQ 7090"), carried out in 96-well microtitre plates (MTPs). The test volume was 100  $\mu$ l and contained 20 mM Tris buffer (pH 7.4), 0.1 mg of BSA (bovine serum albumin)/ml, 5 mM  $Mg^{2+}$ , 0.5  $\mu$ M cAMP (including about 50,000 cpm of [3H]cAMP), 1  $\mu$ l of the respective substance dilution in DMSO and sufficient recombinant PDE10A1 (1000xg supernatant, see above) to ensure that 15-20% of cAMP was converted under said experimental conditions. After a preincubation of 5 min at 37°C, the reaction is started by adding a substrate (cAMP) and the assays

- 46 -

are incubated for a further 15 min; after that, they are stopped by adding SPA beads (50  $\mu$ l). In accordance with the manufacturer's instructions, the SPA beads have previously been resuspended in water and diluted 1:3 (v/v) and added to IBMX (3 mM). After the beads have been sedimented (> 30 min), the MTPs are analyzed in commercially available measuring appliances and the corresponding  $IC_{50}$  values of the compounds for the inhibition of PDE10A activity are determined from concentration-effect curves by means of non-linear regression.

Representative inhibitory values [inhibitory concentration as  $-\log IC_{50}$  (mol/l)] which are determined for the compounds according to the invention are shown in the following table 1, in which the numbers of the compounds correspond to the numbers of the examples.

Particular interesting compounds according to this invention are those compounds mentioned in table 1 below.

**Table 1:** Inhibition of PDE10A activity

Compounds	$-\log IC_{50}$
5, 6, 8, 9, 11, 12, 13, 18, 20, 21, 23, 24, 26 to 35, 37 to 54, 56 to 62, 64 to 67	The inhibitory values of the mentioned Examples lie in the range from 7.01 to 9.58